IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VALIDUS PHARMACEUTICALS, INC., Plaintiff,	)	
v.	)	C.A. No. _____
ACTAVIS SOUTH ATLANTIC LLC, and ACTAVIS, INC., Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Validus Pharmaceuticals, Inc. ("Validus") by its attorneys, for its complaint against Actavis South Atlantic LLC and Actavis, Inc., alleges as follows:

The Parties

1. Plaintiff Validus Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at 119 Cherry Hill Road - Suite 310, Parsippany, New Jersey 07054.

2. Upon information and belief, Defendant Actavis South Atlantic LLC ("Actavis South Atlantic") is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 13800 N.W. 2nd Street, Sunrise, Florida 33325. Upon information and belief, Actavis South Atlantic does business in Delaware.

3. Upon information and belief, Defendant Actavis, Inc. is a corporation organized and existing under the laws of the State of Delaware, and has a principal place of business at 14 Commerce Drive, Suite 301, Cranford, New Jersey 07207. Actavis, Inc. does business in the State of Delaware. Actavis, Inc. is the parent of Actavis South Atlantic, and Actavis South Atlantic is a wholly-owned subsidiary of Actavis, Inc.

4. Upon information and belief, Actavis South Atlantic and Actavis, Inc. (collectively, "Actavis") are in the business of manufacturing, distributing, and selling generic pharmaceutical products, which are copies of products invented and developed by innovator pharmaceutical companies.

5. Upon information and belief, Actavis South Atlantic and Actavis, Inc. collaborated in the research and development of Actavis's Abbreviated New Drug Application ("ANDA") No. 79-180 for carbamazepine extended-release capsules, continue to collaborate in seeking approval of that application from the Food and Drug Administration ("FDA"), and intend to collaborate in the commercial manufacture, marketing, and sale of carbamazepine products, including commercial marketing and sale in the State of Delaware, in the event that FDA approves Actavis's ANDA No. 79-180. Upon information and belief, Actavis South Atlantic and Actavis, Inc. collaborate in the manufacture, marketing, and sale of many pharmaceutical products, including numerous generic prescription drug products manufactured and sold pursuant to an approved abbreviated new drug application, that are marketed and sold to customers in the State of Delaware.

Jurisdiction and Venue

6. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code, for infringement of United States Patent No. 6,977,253 ("the '253 patent"). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

7. Actavis South Atlantic is subject to personal jurisdiction in this judicial district because it is a limited liability company organized and existing under the laws of the State of Delaware and, by virtue of, *inter alia*, its being organized in the State of Delaware,

having availed itself of the rights and benefits of Delaware law, and having engaged in substantial and continuing contacts with the State.

8. Actavis, Inc. is subject to personal jurisdiction in this judicial district because it is a corporation organized and existing under the laws of the State of Delaware and, by virtue of, *inter alia*, its being incorporated in the State of Delaware, having availed itself of the rights and benefits of Delaware law, and having engaged in substantial and continuing contacts with the State.

9. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Regulatory Requirements for Approval of New and Generic Drugs

10. Any person wishing to market a pioneering drug – that is, a new drug that has not previously been approved by FDA – must first file a New Drug Application ("NDA") with FDA demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b). To secure approval of a NDA, the NDA applicant must, among other things, collect and submit to FDA extensive animal and human clinical trial data at a substantial cost of time and money.

11. A person wishing to market a generic copy of a pioneering drug that previously has been approved by FDA may follow a truncated approval process by filing an abbreviated new drug application for a generic version of the drug. In the ANDA, the applicant must demonstrate, among other things, bioequivalence of the generic copy of the pioneering drug. 21 U.S.C. § 355(j)(2)(A)(iv). To demonstrate bioequivalence, the ANDA applicant must show that the rate and extent of absorption of the therapeutic ingredient in the generic drug does not significantly differ from that in the pioneering drug, or, if the rate of absorption differs, that

such difference is intentional, is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. 21 U.S.C. § 355(j)(8)(B).

12. However, unlike a NDA applicant, an ANDA applicant is not required to include safety and effectiveness data. The ANDA applicant is not required, for example, to conduct well-controlled clinical trials concerning the safety and effectiveness of the proposed drug. Instead, the ANDA applicant is permitted to piggy-back on the safety and effectiveness data developed and submitted by the approved NDA holder. 21 U.S.C. § 355(j).

13. Nor does an ANDA applicant establish any new conditions of use for the proposed drug product. Instead, an ANDA applicant may seek approval only for conditions of use that previously have been approved in connection with an approved NDA. 21 U.S.C. § 355(j)(2)(A)(i).

14. No person may market in the United States a new drug without an approved NDA or a generic version of a drug without an approved ANDA. 21 U.S.C. § 355(a).

Plaintiff's Approved Drug Product

15. Validus is the holder of an approved new drug application, NDA No. 21-710, for carbamazepine extended-release capsules. That NDA was approved by FDA on December 10, 2004 and covers three strengths of capsule – 100 mg, 200 mg, and 300 mg. The sole indication or condition of use for which carbamazepine extended-release capsules are approved in NDA No. 21-710 is the treatment of acute manic to mixed episodes associated with Bipolar I disorder.

16. Pursuant to FDA's approval, Validus currently markets carbamazepine extended-release capsules for the treatment of acute manic to mixed episodes associated with Bipolar I disorder under the trademark EQUETRO®.

17. FDA has listed the '253 patent in the Orange Book – formally known as Approved Drug Products With Therapeutic Equivalence Evaluations – in connection with NDA No. 21-710.

18. The '253 patent qualifies for listing in the Orange Book in connection with NDA No. 21-710 because it claims an approved use of the drug product that is the subject of that NDA. Actavis South Atlantic and Actavis have never challenged the listing of the '253 patent in the Orange Book.

Actavis's ANDA

19. Actavis has represented that on or before December 4, 2007, it submitted to FDA an ANDA (ANDA No. 79-180) and paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for carbamazepine extended-release capsules purportedly bioequivalent to Validus's EQUETRO® carbamazepine extended-release capsule products. The purpose of Actavis's ANDA and paragraph IV certifications, is to obtain approval under section 505(j) of the FDCA to engage in the commercial manufacture and sale of its proposed carbamazepine extended-release capsules before the expiration of the patents listed in the Orange Book for Validus's NDA No. 21-710. Hence, Actavis's purpose in submitting ANDA No. 79-180 is to market in the United States the carbamazepine products described therein before expiration of the '253 patent.

20. On or about December 4, 2007, Actavis sent a letter advising Validus of Actavis's paragraph IV certification relating to the '253 patent ("Actavis's Notice Letter"). Actavis's Notice Letter included an offer of confidential access that would permit Validus's outside counsel to review Actavis's ANDA.

21. Upon information and belief, the sole condition of use for which Actavis seeks approval in its ANDA No. 79-180 for its proposed carbamazepine extended-release capsules is the treatment of acute manic to mixed episodes associated with Bipolar I disorder, the same condition of use as that approved in Validus's NDA No. 21-710.

22. Upon information and belief, the sole indication set forth in the proposed labeling submitted by Actavis in its ANDA No. 79-180 for its proposed carbamazepine extended-release capsules is the treatment of acute manic to mixed episodes associated with Bipolar I disorder, the same indication as that set forth in the approved labeling for Validus's EQUETRO® carbamazepine extended-release capsule products.

Count 1: Patent Infringement

23. Validus realleges paragraphs 1 through 22 above as if fully set forth herein.

24. On December 20, 2005, the United States Patent and Trademark Office duly and legally issued the '253 patent, entitled "Methods For The Treatment Of Bipolar Disorder Using Carbamazepine." The term of the '253 patent runs through May 19, 2024. A true and correct copy of the '253 patent is attached hereto as Exhibit A.

25. Validus is the owner of the '253 patent.

26. Validus currently markets carbamazepine extended-release capsule products in the United States under the trademark EQUETRO®. The conditions of use for which EQUETRO® carbamazepine extended-release capsule products are approved fall within one or more of the claims of the '253 patent.

27. Actavis is liable for infringement of the '253 patent under 35 U.S.C. § 271(e)(2)(A) by virtue of its filing ANDA No. 79-180 with a paragraph IV certification seeking FDA approval of ANDA No. 79-180 prior to expiration of the '253 patent.

28. Upon information and belief, the conditions of use for which Actavis seeks approval in its ANDA No. 79-180 fall within one or more of the claims of the '253 patent. Upon information and belief, if approved, use of Actavis's proposed carbamazepine products in accordance with the proposed labeling submitted in ANDA No. 79-180 would infringe one or more of the claims of the '253 patent.

29. Upon information and belief, if ANDA No. 79-180 is approved, Actavis intends to manufacture, use, offer for sale, and sell in the United States, and import into the United States, the carbamazepine products for which approval is sought in Actavis's ANDA No. 79-180.

30. Upon information and belief, if approved, Actavis's carbamazepine products proposed in Actavis's ANDA No. 79-180 will be administered to human patients in a therapeutically effective amount for treatment of acute manic or mixed episodes of Bipolar I disorder, which administration would constitute direct infringement of one or more claims of the '253 patent. Upon information and belief, this infringement will occur at Actavis's behest, with its intent, knowledge, and encouragement, and Actavis will actively induce, encourage, aid, and

abet this administration with knowledge that it is in contravention of Validus's rights under the '253 patent.

31. Actavis's manufacture, use, offer for sale or sale in the United States, or importation into the United States, prior to expiration of the '253 patent, of the carbamazepine products for which approval is sought in ANDA No. 79-180, would actively induce and contribute to infringement of the '253 patent, and Actavis would be liable as an infringer under 35 U.S.C. §§ 271(b) and/or (c).

32. Validus will be irreparably harmed if Actavis is not enjoined from infringing or actively inducing or contributing to infringement of the '253 patent. Validus does not have an adequate remedy at law.

Prayer For Relief

WHEREFORE, Plaintiffs seek the following relief:

A. A judgment that Actavis has infringed one or more claims of the '253 patent under 35 U.S.C. § 271(e)(2)(A).

B. A judgment and order pursuant to 35 U.S.C. § 271(e)(4) providing that the effective date of any FDA approval of the Actavis ANDA No. 79-180 for carbamazepine extended-release 200 mg and 300 mg capsules be not earlier than the expiration date of the '253 patent;

C. A judgment declaring that Actavis's manufacture, use, offer for sale, or sale in the United States, or importation into the United States, of the carbamazepine products for which approval is sought in ANDA No. 79-180 would induce or contribute to infringement of the '253 patent, pursuant to 35 U.S.C. § 271 (b), and/or (c);

D. A permanent injunction enjoining Actavis and its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from making, using, selling, or offering to sell in the United States, or importing into the United States, the carbamazepine extended-release capsules for which approval is sought in ANDA No. 79-180, or any carbamazepine product that induces or contributes to the infringement of the '253 patent, until expiration of that patent;

E. A finding that this is an exceptional case, and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;

F. An award of costs and expenses in this action; and

G. Such further and other relief as this Court determines to be just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

Jack B. Blumenfeld (#1014)
Maryellen Noreika (#3208)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@mnat.com
mnoreika@mnat.com

Attorneys for Plaintiff

Of Counsel:

George F. Pappas
Roderick R. McKelvie
Jeffrey B. Elikan
Steven P. Berman
Sarah J. Chickos
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
(202) 662-6000

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EXHIBIT A

US006977253B2

(12) **United States Patent**
Kalali et al.

(10) **Patent No.: US 6,977,253 B2**
(45) **Date of Patent: Dec. 20, 2005**

(54) **METHODS FOR THE TREATMENT OF BIPOLAR DISORDER USING CARBAMAZEPINE**

(75) Inventors: **Amir H. Kalali**, San Diego, CA (US); **Simon J. Tulloch**, Gaithersburg, MD (US)

(73) Assignee: **Shire Pharmaceutical Development Inc.**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/848,383**

(22) Filed: **May 19, 2004**

(65) **Prior Publication Data**

US 2005/0124601 A1 Jun. 9, 2005

Related U.S. Application Data

(60) Provisional application No. 60/527,298, filed on Dec. 8, 2003.

(51) **Int. Cl.**[7] **A61K 31/55**
(52) **U.S. Cl.** **514/217**; 514/212
(58) **Field of Search** 514/217, 212

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Primary Examiner—Sreenivasan Padmanabhan
Assistant Examiner—Jennifer Kim
(74) *Attorney, Agent, or Firm*—Millen, White, Zelano, Branigan, P.C.

(57) **ABSTRACT**

Carbamazepine, in extended release form, is useful in the treatment of patients suffering from bipolar disorder. In order to minimize the time it takes to reach efficacy, carbamazepine, in extended release form, can be administered to the patient at an initial daily dose which is then increased in daily increments until clinical efficacy is achieved.

34 Claims, 3 Drawing Sheets

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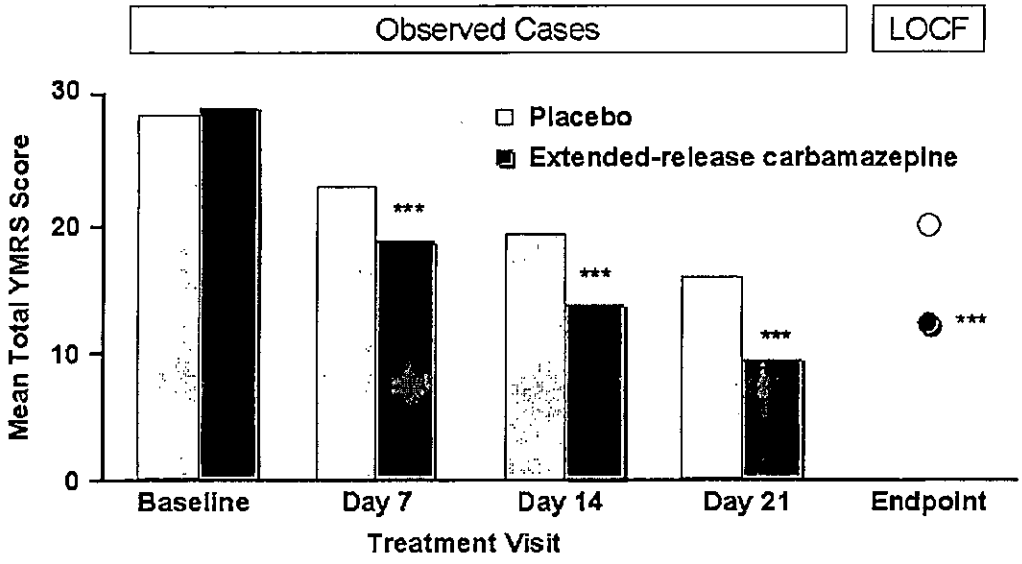
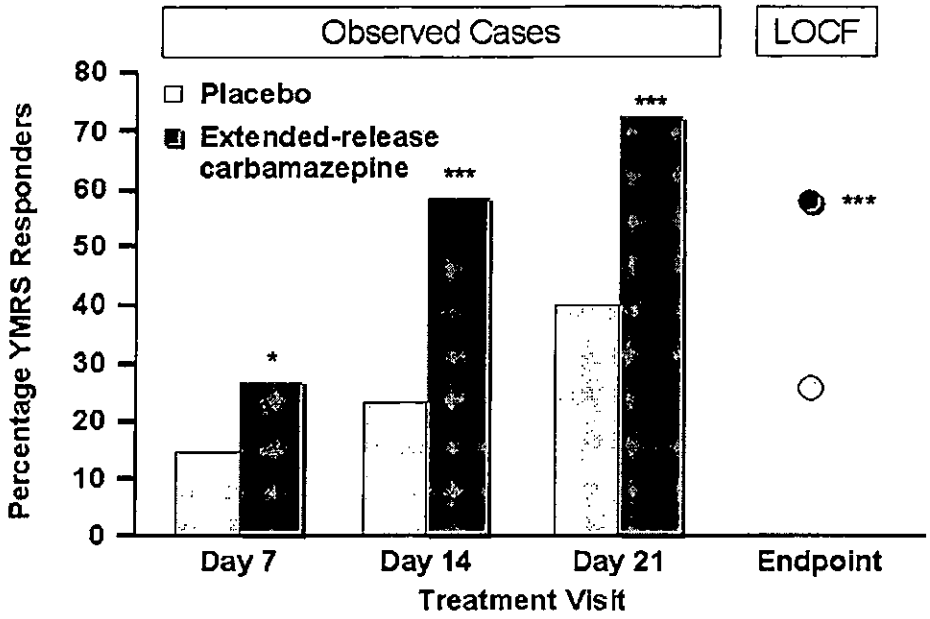
Figure 1. Mean YMRS total scores for extended-release carbamazepine patients (ITT population)



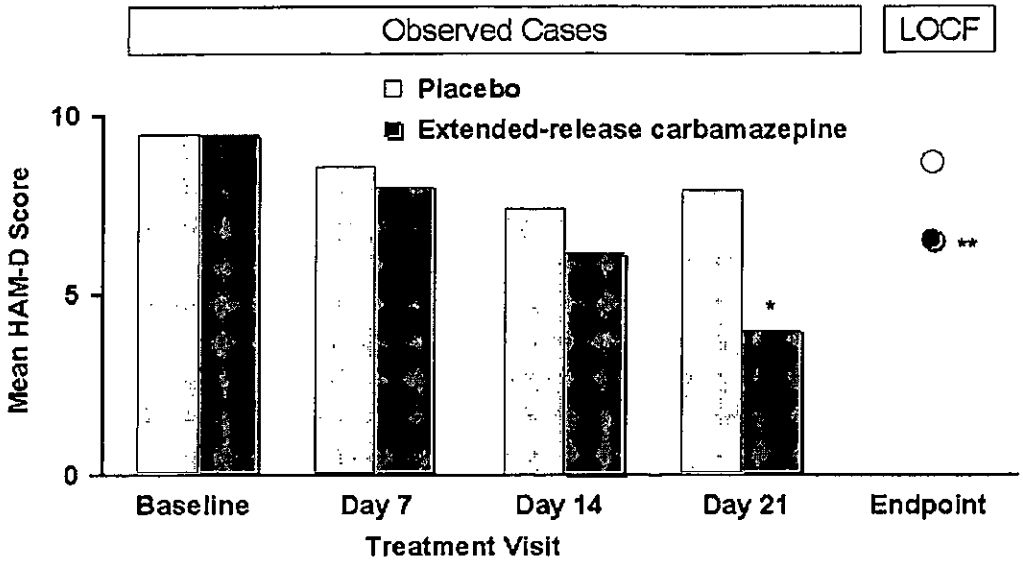
***$P < .001$ compared to placebo following ANCOVA with baseline score as covariate.
Data on file, Shire Pharmaceutical Development.

Figure 2. Increased percent responders (>50% YMRS) on extended-release carbamazepine (ITT population)



*P = .0286, ***P < .001 compared to placebo following ANCOVA with baseline score as covariate. Data on file, Shire Pharmaceutical Development.

Figure 3. Significant reduction in HAM-D score on extended-release carbamazepine (ITT population)



*P = .002, **P = .008 compared to placebo following ANCOVA with baseline score as covariate.
Data on file, Shire Pharmaceutical Development.

METHODS FOR THE TREATMENT OF BIPOLAR DISORDER USING CARBAMAZEPINE

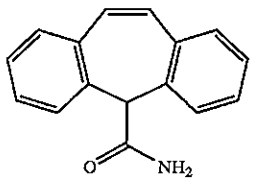
This application claims the benefit of U.S. provisional patent application Ser. No. 60/527,298, filed Dec. 8, 2003.

FIELD OF THE INVENTION

The present invention relates to methods of treating bipolar disorder in patients using extended release formulations of carbamazepine wherein the dosage regimen has an initial rapid titration period.

BACKGROUND OF THE INVENTION

Carbamazepine, or 5-carbamoyl-5H-dibenz(b,f)azepine (or 5H-dibenz(b,f)azepine-5-carboxamide or N-carbamoyliminostilbene), is an iminostilbene derivative which is a known analgesic and anticonvulsant used for the treatment of epilepsy, the pain associated with trigeminal neuralgia, psychomotor and grand mal seizures, and neurological disorders such as chronic pain states and headaches. Additionally, carbamazepine is used in various psychiatric disorders such as bipolar disorder, depression, cocaine addiction, alcohol addiction, opiate addiction, nicotine addiction, other obsessive compulsive disorders and cardiovascular disease.



Carbamazepine

Carbamazepine and its synthesis are described in U.S. Pat. No. 2,948,718. Other processes for synthesizing carbamazepine are described in EP 0 029 409, EP 0 277 095, EP 0 688 768, EP 0 423 679, and EP 0 485 685.

Carbamazepine extended-release formulations have been developed in recent years to decrease daily fluctuations in serum carbamazepine concentration by smoothing out bloods levels of the drug and to improve dosing convenience. These extended-release formulations are typically designed to provide carbamazepine at a therapeutic range of from about 4 μg/ml to about 12 μg/ml of carbamazepine over a period of time. Blood levels of carbamazepine of less than 4 μg/ml have been found to be ineffective in treating clinical disorders while blood levels greater than 12 μg/ml have been found to be likely to result in undesirable side effects such as neuromuscular disturbances, cardiovascular and gastrointestinal effects.

SPD417 and Carbatrol® (both from Shire US Inc., Newport, Ky.) are extended-release preparations of carbamazepine which has allowed for twice daily administration of the drug in patients (See U.S. Pat. No. 5,326,570 and U.S. Pat. No. 5,912,013 which describe the formulation of carbamazepine). Currently, Carbatrol® is approved by the FDA for use in the treatment of epilepsy and pain associated with trigeminal neuralgia. For treating epilepsy, the usual initial dose for adults and children over 12 years of age is 200 mg taken twice daily. The dosage is then increased at weekly intervals by adding 200 mg/day. The dosage should generally not exceed 1,000 mg daily in children 12 to 15 years old and 1,200 mg daily for adults and children over 15 (dosages up to 1600 mg daily have been used for adults. For maintenance, the daily dosage is generally 800 to 1,200 mg. For treating trigeminal neuralgia, the usual dose is 200 mg on the first day and may be increased by up 200 mg every 12 hours as needed to achieve freedom from pain. The doses should not exceed 1,200 mg daily and the maintenance dose is usually in the range of 400 mg to 800 mg.

Tegretrol-XR® is another extended release, oral formulation of carbamazepine (sold by Novartis Pharmaceuticals) which is approved by the FDA for the treatment of epilepsy and the pain associated with trigeminal neuralgia. The suggested dosage regimens for Tegretrol-XR® are the same as for the Carbatrol® extended release formulation.

The range of therapeutic options for bipolar disorder has included in recent years several anticonvulsants and antipsychotic medications. Carbamazepine, a major antiepileptic drug used in treating convulsive, simple and complex partial seizures, has also long been considered one of the standard therapies for bipolar disorder, although it is not approved for this use by the FDA (drugs currently approved by FDA for the treatment of acute mania include lithium, valproate, chlorpromazine, olanzapine and lamotrigine). See, e.g., Okuma et al., "Anti-Manic and Prophylactic Effects of Carbamazepine (Tegretol®) on Manic Depressive Psychosis," Folia Psychiatrica et Neurologica Japonica, 27:4, pp. 283–297 (1973); Okuma et al., "Comparison of the Antimanic Efficacy of Carbamazepine and Chlorpromazine in Mania: A Double-Blind Trial," Psychopharmacology, 66, pp. 211–217 (1979); Grossi et al., "Carbamazepine vs Chlorpromazine: A Double-Blind Controlled Study," in: Emrich et al. (eds) Anticonvulsants in Affective Disorders, Princeton, N.J., Excerpta Medica, pp. 177–187 (1984); Lerer et al, "Carbamazepine Versus Lithium in Mania: A Double-Blind Study," J. Clin. Psychiatry, 48:3, pp. 89–93 (1987); Okuma et al., "Comparison of the Antimanic Efficacy of Carbamazepine and Lithium Carbonate by Double-Blind Controlled Study," Pharmacopsychiatry, 23, pp. 143–150 (1990); and Keck et al., "Carbamazepine and Valporate in the Maintenance Treatment of Bipolar Disorder," J. Clin. Psychiatry, 63 (Suppl 10), pp. 13–17 (2002).

However, in the treatment of bipolar disorder, carbamazepine has been used mainly in immediate-release preparations which need to be administered three or four times daily to avoid potentially problematic serum drug fluctuations. Also, in these treatments, carbamazepine has generally been administered at a constant dosage (see, e.g., Okuma et al. (1973)), at an initial constant dosage with subsequent adjustment (see, Okuma et al. (1979)), or at a gradually increasing dosage (See, e.g., Lerer et al. (1987)).

As described above, the generally accepted method for administering extended-release carbamazepine in the treatment of epilepsy has been to initiate a patient with 200 mg/day twice daily of carbamazepine with weekly increases of up to 200 mg/day until the optimal response was obtained. This dosage regime has also been used for the treatment of bipolar disease. Despite the treatments which are presently available with carbamazepine, there is a need to treat bipolar disorder using a more rapid treatment period than that which has been previously used.

Goldberg et al. [J. Clin. Psychiatry, 59:4, pp. 151–158, April 1998] reports the results of a retrospective study comparing the time to remission for pure and mixed manic bipolar patients who were treated with lithium, carbamazepine, divalproex, or combinations thereof. Of the 120 subjects included in this study, only 7 subjects took carbam-

azepine alone (4 mixed manic; 3 pure manic). Goldberg et al. conclude that the time course to remission "appears to be strongly influenced by the speed which patients achieve a therapeutic serum level of an antimanic agent." In the study, the minimum therapeutic serum level for carbamazepine was ≧8 μg/mL. Goldberg et al. do not describe the dosage regimens used in the study for administering carbamazepine.

Vasudev et al. [Psychopharmacology, 150:15–23 (2000)] report the results of a study comparing carbamazepine and valproate monotherapies. In the study, carbamazepine was given orally in the form of 200 mg tablets. The subjects treated with carbamazepine were initially given 400 mg/day in two divided doses. The dose was then increased by 200 mg/day or 400 mg/day for the next two days. Thereafter, the dose was increased 200–400 mg at weekly intervals. This was continued until clinical improvement occurred, or a serum level not exceeding 14 μg/ml was reached, or dose limiting adverse effects occurred. The therapeutic serum level window used in the study for carbamazepine was 6–12 μg/ml. In the study, favorable clinical responses were considered responses that showed a more than 50% fall in YMRS scores from baseline. Vasudev et al. conclude from the results of the study that both carbamazepine and valproate monotherapies are feasible but the valproate monotherapy is more efficacious.

Bipolar disorder is a brain disorder which causes unusual shifts in a person's mood, energy and ability to function. The symptoms of bipolar are quite severe and can even result in suicide. Therefore, there remains a need for methods of treating bipolar disorder with carbamazepine that provide efficacy while minimizing the time it takes for the patient to reach efficacy and thus providing an effective method of treating bipolar disorder.

SUMMARY OF THE INVENTION

In accordance with the invention, there is provided a method of treating a patient suffering from bipolar disorder wherein the patient is administered an initial dosage of carbamazepine, in an extended release formulation, and then the dosage is titrated, specifically increased by daily increments, until clinical efficacy is achieved. Thereafter, the patient can be given a daily maintenance dosage which is the same or about the same as the final dosage at the end of the titration period or is a lower daily dosage.

According to an embodiment of the invention, there is provided a method which comprises administering to a bipolar patient an initial daily dose of carbamazepine (e.g., 400 mg) in extended release form and then increasing the dose by daily increments (e.g., 200 mg/day) until clinical efficacy is achieved.

According to another embodiment of the invention, there is provided a method which comprises administering to a patient suffering from bipolar disorder an initial daily dose of carbamazepine in extended release form and increasing the dose by daily increments until clinical efficacy is achieved, wherein the occurrence of adverse side effects is not greater than that which occurs when the daily dose is increased in weekly increments.

According to a further embodiment of the invention, there is provided a method for treating a patient suffering from bipolar disorder comprising administering to the patient an initial daily dose of 100–800 mg carbamazepine in extended release form and increasing the daily dose by increments of 100–400 mg until clinical efficacy is achieved. Total daily dose should, preferably, not exceed 1,600 mg.

According to another aspect of the invention, the titration period, which includes the initial daily dose, is at least 5 days, preferably at least 6 days, especially at least 7 days. For example, clinical efficacy is achieved after at least 7 days, that is the period of time during which the daily dose is increased by increments is at least 6 days.

According to another aspect of the invention, after clinical efficacy is achieved, the treatment is continued by administering to the patient the same daily dose as at which clinically efficacy was achieved or by reducing the daily dose, for example, by daily increments to a dosage level which is lower than that at which clinical efficacy was achieved, whereby efficacy can be maintained. According to a further aspect of the invention, the maintenance dosage following the titration period is 100–1600 mg/day, for example, 800–1,000 mg/day.

The methods according to the invention can be used to treat patients with bipolar disorder who experience manic episodes and/or mixed episodes. Furthermore, the methods can be used to treat patients with bipolar disorder II.

As used in this application, the term "bipolar disorder" represents a disorder which causes dramatic mood swings, from episodes of mania to depression. Bipolar disorder represents manic-depressive disorder, bipolar disorder I (symptoms include alternating episodes of mania and depression), bipolar disorder II (symptoms include alternating hypomanic and depressive episodes), rapid-cycling bipolar disorder (occurs when four or more episodes of illness occur within a 12 month period in a patient) and all other types of depressive and mood disorders that are well known by those of skill in the art.

In accordance with an aspect of the methods of the invention, carbamazepine is preferably administered twice daily. The initial daily dose is, for example, 200 mg, 400 mg, 600 mg or 800 mg, preferably 400 mg. During the titration period, the daily incremental increase in daily dose is, for example, 100 mg, 200 mg, 300 mg or 400 mg, preferably 200 mg.

In accordance with an aspect of the methods of the invention, carbamazepine is preferably administered once daily. The initial daily dose is, for example, 100 mg, 200 mg, 300 mg or 400 mg. During the titration period, the daily incremental increase in daily dose is, for example, 100 mg, 200 mg, 300 mg or 400 mg.

In accordance with the present invention, extended release formulations of carbamazepine can be administered sublingually, transmucosally, transdermally, parenterally and orally. Suitable dosage forms include but are not limited to liquids, tablets, capsules, sprinkle dosage forms, chewable tablets, pellets and transdermal patches. Oral administration is preferred, preferably in the form of capsules, such as described in U.S. Pat. No. 5,326,570 and U.S. Pat. No. 5,912,013, which are hereby incorporated by reference.

In the context of the invention, evaluation of efficacy can be performed by use of the Young Mania Rating Scale (YMRS). On this scale, normalcy is associated with a rating of approximately 5 to 10. A rating above 20 is considered to be indicative of abnormalcy. Thus, using this scale, clinical efficacy occurs when there is at least a 50% reduction in a YMRS score from the baseline determined prior to the initiation of dosing.

It is to be understood that other means could be used for determining clinical efficacy, such as CGI (clinical global impression scale). Another endpoint for efficacy which could be used in patients that have depressive symptoms is HDRS (or HAM-D).

In accordance with the invention, carbamazepine can be used as a monotherapy for treating bipolar disorder. Alternatively, the inventive method can be used in conjunction with treatments that use other agents such as lithium, valproate, chlorpromazine, olanzapine, lamotrigine, and gabapentin.

The entire disclosures of all applications, patents and publications cited above are hereby incorporated by reference.

EXAMPLE 1

A multicenter, placebo-controlled, double-blind, randomized clinical trial was conducted to evaluate the efficacy and safety of monotherapy with extended-release carbamazepine capsules (SPD417, supplied by Shire US Inc., Newport, Ky.) in bipolar disorder patients with manic and mixed episodes.

Subjects

The subjects enrolled in this study were at least 18 years of age and met DSM-IV criteria for bipolar I disorder with most recent manic or mixed episodes. A history of at least 1 previous manic or mixed episode and minimum screen and baseline total score of 20 on the Young Mania Rating Scale (YMRS) was required, as per the YMRS rating scale reported in Young R C, Biggs J T, Ziegler V E, et al., *Br J Psychiatry,* 1978; 133: 429–435. The patients were not eligible to enroll in this study if they had been treated with electroconvulsive therapy (ECT) or clozapine within 3 months of baseline or antidepressants within 4 weeks of baseline. Concomitant therapy with antidepressants, antipsychotics, lithium, ECT, or anxiolytic or sedative-hypnotic drugs was prohibited, with the exception of lorazepam which may have been used for agitation or sleep.

Methods

A 21-day randomized, double-blind, placebo-controlled study was conducted followed by a 5-day single-blind placebo lead-in period. Treatment with extended-release carbamazepine was initiated at 200 mg twice a day and titrated by increments of 200 mg/day to final doses between 200 mg/day and 1600 mg/day, as necessary and tolerated. Efficacy was assessed weekly with the YMRS, Clinical Global Impression (CGI) scales, Hamilton Depression Rating Scale (HAM-D or HDRS). Each week, adverse events (AEs) and compliance was recorded. The primary efficacy outcome measure was the change from baseline to last observation in the YMRS total score. Secondary efficacy assessments included responder rate (percentage of patients with at least a 50% decrease in YMRS scores from baseline to last observation), change from baseline to last observation in Clinical Global Impression (CGI) and in the 21-Item Hamilton Rating Scale for Depression (HAM-D), depressed mood item score, and time-to-outpatient status.

Data Analysis

All statistical analyses were carried out using SAS windows (version 8.0). SAS Type III estimation was utilized, and the significance level was set at 0.05 for all statistical tests. The primary efficacy end point was the last observation carried forward (LOCF) value of the decrease from baseline in YMRS total score at day 21 of double-blind treatment for the intent-to-treat (ITT) population. The YMRS total score, HAM-D total score, HAM-D depressed mood item score, and CGI severity score at each post-randomization visit and endpoint were analyzed using a two-way analysis of covariance (ANCOVA) model with treatment and site as the main factors and the baseline value as the covariate for the ITT population. A two-way analysis of variance (ANOVA) was performed on baseline data for these variables with treatment and site as the main factors. The number of subjects with a CGI improvement score, the number of subjects demonstrating a response at each post-randomization visit (Days 7, 14, and 21), and the number of subjects showing a sustained response were analyzed using the Chi-square test with continuity adjustment. Fisher's exact test was used to compare AEs of incidence greater than or equal to 1% between treatment groups.

Results

At 25 study sites, 239 patients were randomized to double-blind treatment, and 144 completed the study. Early discontinuation rates were not significantly different and reasons for the discontinuations were similar between the two treatment groups. There were no important differences between the treatment groups in any demographic and disease diagnosis characteristics at baseline in the randomized subjects and the ITT population. It is to be noted that in the present study, in the diagnosis of the recent bipolar disorder, more subjects had manic bipolar disorder (that is, 79% manic vs. 21% mixed mania).

Treatment-Emergent AEs

As can be seen in Table 1, the most frequently reported treatment emergent serious AEs in the extended-release carbamazepine group were dizziness (39.3%), somnolence (30.3%), and nausea (23.8%). Adverse events reported in this study were typical of those reported in previous trials of carbamazepine in epilepsy and bipolar disorder. The incidence of serious adverse events (SAEs) was similar between the two treatment groups (extended-release carbamazepine: four subjects, six events; placebo: six subjects, six events). Of the ten subjects who experienced a SAE during the double-blind treatment period, seven subjects (three extended-release carbamazepine and four placebo) discontinued the study due to a SAE.

Final Daily Dose of Study Medication

From the 235 ITT subjects of this study, 4.7% had a final daily dose of extended-release carbamazepine of 200 mg, 30.6% had a final daily dose of 400–600 mg, 38.7% had final daily dose of 800–1000 mg, 6.4% had a final daily dose of 1200–1400 mg, and 19.6% had a final daily dose of 1600 mg. Most placebo subjects had a final daily dose of 800–1000 mg (53.9%) or 1600 mg (29.6%).

Efficacy

As can be seen in FIG. 1, the patients treated with extended-release carbamazepine had significantly greater decreases in YMRS total scores compared to patients receiving placebo beginning at week 1 and at primary end point, day 21. In this study, day 7 was the first time point at which efficacy measures were performed, and this early improvement can be compared to results from trials of atypical antipsychotic medications in acute mania.

Surprisingly, the treatment regimen as conducted in the present study (initially 200 mg twice a day and titrated by increments of 200 mg/day to final doses between 200 mg/day and 1600 mg/day) enabled the patients to achieve significant improvements in YMRS and CGI scores beginning on day 7.

FIG. 2 depicts YMRS response rates (patients showing a decrease in YMRS total score of at least 50%) at different time points during the study. Patients treated with extended-release carbamazepine had significantly higher response rates than patients treated with placebo at day 7 (P=0.0286), day 14 day 21 (P<0.0001), and endpoint (P<0.0001). Com-

pared to placebo, extended-release carbamazepine treatment was associated with significantly improved scores on both the CGI improvement and CGI severity scales at day 7 (both P<0.01), as well as on days 14, 21 and at endpoint (all P<0.0001), using LOCF analysis.

It can be seen from FIG. **2**, that at end point (Day 14), 60.8% of extended-release carbamazepine-treated patients were considered YMRS responders (vs. 28.7% with placebo; P<0.0001). In a review of controlled carbamazepine monotherapy trials in acute mania, the pooled response rate was reported to be 52%. Reference: McElroy S L, Keck P E, Jr. Pharmacologic agents for the treatment of acute bipolar mania. Biol Psychiatry 2000; 48: 539–557

HAM-D total score, as can be seen in FIG. **3**, was also significantly improved in extended-release carbamazepine-treated patients compared to placebo-treated patients both on day 21 (P=0.002) and at endpoint (P=0.008). At day 21, although only a small group of patients were evaluated for depressive symptoms, the results are statistically significant in showing that the depressive symptoms were subsiding with the extended-release carbamazepine.

The results indicate that monotherapy with extended-release carbamazepine capsules was effective and safe for the treatment of bipolar patients with manic or mixed episodes in this multicenter, randomized, double-blind, placebo-controlled trial. Patients treated with extended-release carbamazepine had significantly greater improvements on the YMRS, CGI-I, CGI-S, and HAM-D scales than those treated with placebo. The above-results show for the first time in a placebo-controlled study that extended-release carbamazepine administered in a daily dosing schedule produces clinical improvement with satisfactory tolerability and safety in patients with bipolar disorder.

EXAMPLE 2

A similar dosing regimen could be used for conducting a study of efficacy and safety of monotherapy with extended-release carbamazepine in bipolar disorder patients with manic and mixed episodes by administering the drug 100 mg to 400 mg once a day and titrated in increments of 100 to 400 mg/day to final doses between 100 mg/day and 1600 mg/day, as necessary and tolerated.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

TABLE 1

Notable Treatment-Emergent Adverse Events*

AEs	Extended-release carbamazepine (n = 122) n (%)	Placebo (n = 117) n (%)
Any†	112 (91.8)	66 (56.4)
Dizziness†	48 (39.3)	14 (12.0)
Somnolence†	37 (30.3)	12 (10.3)
Nausea†	29 (23.8)	11 (9.4)
Headache	25 (20.5)	15 (12.8)
Ataxia†	23 (18.9)	0
Vomiting†	20 (16.4)	3 (2.6)

TABLE 1-continued

Notable Treatment-Emergent Adverse Events*

AEs	Extended-release carbamazepine (n = 122) n (%)	Placebo (n = 117) n (%)
Dyspepsia	16 (13.1)	13 (11.1)
Blurred Vision†	11 (9.0)	2 (1.7)
Pain	9 (7.4)	12 (10.3)

*Treatment-emergent adverse events reported by more than 10% of patients in either treatment group or significantly different between treatment groups.
†Treatment-emergent adverse events with a significant difference between treatment groups

What is claimed is:

1. A method of treating a patient suffering from bipolar disorder comprising administering to said patient an initial daily dose of 100–800 mg of carbamazepine in extended release form and increasing said dose by daily increments of 100–400 mg until clinical efficacy is achieved, wherein the occurrence of adverse side effects is not greater than that which occurs when the daily dose is increased in weekly increments.

2. A method of treating a patient suffering from bipolar disorder comprising administering to said patient an initial daily dose of 100–800 mg carbamazepine in extended release form and increasing said daily dose by daily increments of 100–400 mg until clinical efficacy is achieved.

3. A method according to claim **2**, wherein said method is used to treat a patient that suffers from manic episodes.

4. A method according to claim **2**, wherein said method is used to treat a patient that suffers from mixed episodes.

5. A method according to claim **2**, wherein carbamazepine is administered twice daily.

6. A method according to claim **2**, wherein said initial dose is 200 mg.

7. A method according to claim **2**, wherein said initial dose is 400 mg.

8. A method according to claim **2**, wherein said initial dose is 600 mg.

9. A method according to claim **2**, wherein said initial dose is 800 mg.

10. A method according to claim **2**, wherein the daily dose increment is 100 mg.

11. A method according to claim **2**, wherein the daily dose increment is 200 mg.

12. A method according to claim **2**, wherein the daily dose increment is 300 mg.

13. A method according to claim **2**, wherein the daily dose increment is 400 mg.

14. A method according to claim **2**, further comprising administering to said patient lithium, valproate, chlorpromazine, olanzapine, lamotrigine, gabapentin or a combination thereof.

15. A method according to claim **1**, wherein the period of time during which the daily dose is increased daily by increments is at least 6 days.

16. A method according to claim **1**, further comprising continuing to treat said patient by administering the same daily dose as at which clinically efficacy is achieved or reducing said daily dose by daily increments to a lower level at which efficacy can be maintained.

17. A method according to claim **2**, wherein the period of time during which the daily dose is increased by daily increments is at least 6 days.

18. A method according to claim 2, further comprising continuing to treat said patient by administering the same daily dose as at which clinically efficacy is achieved or reducing said daily dose by daily increments to a lower level at which efficacy can be maintained.

19. A method of treating a patient suffering from bipolar disorder comprising administering to said patient an initial daily dose of 100–800 mg of carbamazepine in extended release form and increasing said dose by daily increments until a final daily dose of 1,000–1,600 mg.

20. A method according to claim 19, wherein said initial daily dose is 100–400 mg.

21. A method according to claim 19, wherein said final daily dose is 1,200–1,600 mg.

22. A method according to claim 21, wherein said final daily dose is 1,200–1,400 mg.

23. A method according to claim 19, wherein said initial daily dose is 200 mg.

24. A method according to claim 21, wherein said initial daily dose is 200 mg.

25. A method according to claim 22, wherein said initial daily dose is 200 mg.

26. A method according to claim 19, wherein said initial daily dose is 400 mg.

27. A method according to claim 21, wherein said initial daily dose is 400 mg.

28. A method according to claim 22, wherein said initial daily dose is 400 mg.

29. A method according to claim 1, wherein the period of time during which the daily dose is increased by daily increments is at least 5 days.

30. A method according to claim 2, wherein the period of time during which the daily dose is increased by daily increments is at least 5 days.

31. A method according to claim 19, wherein the period of time during which the daily dose is increased by daily increments is at least 5 days.

32. A method according to claim 1, wherein carbamazepine is administered twice daily, the initial daily dose is 400 mg, and the daily dose increment is 200 mg.

33. A method according to claim 2, wherein carbamazepine is administered twice daily, the initial daily dose is 400 mg, and the daily dose increment is 200 mg.

34. A method according to claim 19, wherein carbamazepine is administered twice daily, the initial daily dose is 400 mg, and the daily dose increment is 200 mg.

* * * * *

JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

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Validus Pharmaceuticals, Inc.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Maryellen Noreika, MORRIS, NICHOLS, ARSHT & TUNNELL LLP,
1201 North Market Street, P.O. Box 1347,
Wilmington, DE 19899-1347, (302) 658-9200

DEFENDANTS
Actavis South Atlantic LLC and
Actavis, Inc.

County of Residence of First Listed Defendant _____
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Attorneys (If Known)

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- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

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PERSONAL INJURY
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- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
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- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
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- ☐ 620 Other Food & Drug
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- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
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SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
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- ☐ 864 SSID Title XVI
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OTHER STATUTES
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- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
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- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing (**Do not cite jurisdictional statutes unless diversity**):
35 U.S.C. § 271

Brief description of cause: Patent infringement

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE 1/17/08

SIGNATURE OF ATTORNEY OF RECORD Maryellen Noreika

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

08-036

Civil Action No. _____

FILED
CLERK, U.S. DISTRICT COURT
DISTRICT OF DELAWARE
2008 JAN 17 PM 12:36

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 3 COPIES OF AO FORM 85.

JAN 17 2008
(Date forms issued)

(Signature of Party or their Representative)

ZACHARY MICHAEL BERL
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action